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Mitoxantrone in Advanced Renal Cancer: a Phase II Study in Previously Untreated Patients from the EORTC Genito-Urinary Tract Cancer Cooperative Group

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Abstract—*Mitoxantrone at a dose of* 15 mg/m^2 *i.v. q* 3 weeks *failed to produce responses in* 29 *adequately treated patients with measurable advanced renal cell carcinoma. The side-effects observed in this group of patients with a good performance status were generally mild. On the basis of this negative result, the application of mitoxantrone in this disease is not recommended.*

INTRODUCTION

THE RESULTS of treatment of advanced renal cell carcinoma have been universally poor. The regression of metastases following nephrectomy is unusual and surgery has little or no effect on survival [1]. Hormonal therapy has proved disappointing [2] and recent reports only confirm the lack of response [3]. Radiotherapy is at best palliative. The suggestions that immunocompetence might be of particular relevance in this tumor continue to encourage the application of tissue-specific and non-specific immunotherapy alone and in combination with chemotherapy [4–6], but the value of this modality has yet to be established. A variety of chemotherapeutic agents have been tested and proven to be ineffective [7, 8].

Recently, the EORTC Genito-Urinary Tract Cancer Cooperative Group started a single-agent phase II screening program. The first drug to be studied was methylglyoxal-bis-guanylhydrazone. It showed limited activity of short-term duration [9]. The second drug tested was vindesine, which even failed to produce any responses [10]. The next cytotoxic drug studied was mitoxantrone.

Mitoxantrone (dihydroxyanthracenedione) is one of a series of anthracenedione derivatives synthesized as part of the search for compounds which retain the antitumor efficacy of the anthracycline compounds in current use but have less (or no) associated cardiotoxicity. In experimental tumors mitoxantrone has a spectrum of activity similar to that of adriamycin [11], while studies in beagle dogs have shown it to be less cardiotoxic [12]. In phase I studies the compound was found to be well tolerated, being relatively free from side-effects such as nausea, vomiting and alopecia. Leucopenia was the dose-limiting toxicity [13].

In phase II studies mitoxantrone has been shown to have significant activity in patients with advanced breast cancer [14–16] and in patients with non-small cell lung cancer and melanoma [14]. During the third EORTC–NCI symposium on new drugs in December 1981 some hints of activity of the drug in advanced renal cell cancer were reported [17, 18]. Therefore we initiated this phase II study.

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MATERIALS AND METHODS

Between March 1982 and February 1983 fourteen institutions entered 43 patients with histologically proven, progressive, measurable, advanced renal cell cancer into a phase II study using mitoxantrone (15 mg/m^2) i.v. once every 3 weeks. The eligibility criteria were very strict: age $\leqslant$65 yr, WHO performance status $\leqslant$1, no previous chemotherapy, hormonal therapy stopped for at least 6 weeks, no second tumor, no brain metastasis, no radiotherapy to any indicator lesion, white blood cell (WBC) count $\geqslant 4 \times 10^9$/l, platelet count $\geqslant 125 \times 10^9$/l with adequate cardiac, kidney and hepatic function.

Pretreatment studies included physical examination, blood cell count, serum creatinine analysis, liver function tests and chest X-ray.

The evaluation of response and toxicity was performed using WHO criteria [19]. Computerized tomography and ultrasound echography were accepted as means of measuring indicator lesions. The doses of mitoxantrone were modified by 10% if myleotoxicity grade I and 25% if myelotoxicity grade II was observed on the day of retreatment. If grade III toxicity (WBC $<2.0 \times 10^9$/l and/or platelet $<50 \times 10^9$/l) was observed the treatment was postponed until at least grade II toxicity was reached, and the dose then given was modified according to the rules given above. If no myelotoxicity was observed after two courses and the disease was not progressive the dose of mitoxantrone was escalated by 2 mg/m^2.

RESULTS

Eight of the entered patients proved to be ineligible: two were too old, two had a performance status of 2, three had prior chemotherapy and one had no measurable lesion. Of the 35 eligible patients the median age was 57 (32–66 yr), 23 had a performance status 0, 12 had a performance status 1 and there were 26 males and 9 females.

Further patient characteristics are shown in Table 1. Twenty-nine patients were fully evaluable for both response and toxicity. Out of the six patients who were considered not fully evaluable, three were given too low a dose and three had only one course because their disease progressed rapidly. The protocol required that patients receive at least two courses to be fully evaluable.

Table 1. Patient characteristics

	No. of patients
Registered patients	43
Ineligible patients	8
Evaluable patients	35
Prior treatment:	
No treatment	6
Surgery only	24
Surgery + radiotherapy	1
Surgery + hormone therapy	4
Marker lesions:	
Lung only	27
Lung + skin	1
Lung + primary	2
Soft tissue met	1
Local in scar	2
Subcutaneous	1
Retroperitoneal	1

Response to treatment

The 29 fully evaluable patients received between 2 and 11 courses (mean, 3.8; median, 3). No complete or partial responses were observed. In 14 patients the disease remained stable and in 15 progression was reported. It must be mentioned that in all 14 patients who remained stable, progressive disease during the last 2 months prior to entry existed. As previously mentioned, three additional patients had progressive disease after one course.

Toxicity of the treatment

Mitoxantrone was generally well tolerated. A total of 32 patients were evaluable for toxicity and received 112 treatment cycles.

Of the non-hematological side-effects transient nausea and vomiting were the most common, adverse effects occurring in 72% (23/32) of the patients. Moderate, patchy alopecia was reported by two patients, while five other patients reported minimal hair loss. Oral toxicity (mucositis) was found in five patients (soreness, 3; slight ulceration, 1; heavy ulceration, 1).

The only observed hematological side-effect was leukopenia. In fact, leukopenia, defined as WBC <3000, was observed in eight patients and in an additional seven patients the observed leukopenia was even less than 2000. Dose reduction and/or delay of treatment because of leukopenia was necessary in six patients. Finally, the protocol asked for dose escalation, which could be performed in seven patients to 17 mg/m^2 and in one to 19 mg/m^2.

DISCUSSION

No response to mitoxantrone in this group of advanced renal cell cancer patients has been observed. The preliminary reports from De Jager *et al.* [17] and Gams *et al.* [18] about activity could not be confirmed, although patient selection criteria permitted an optimal chance for the drug to show its activity: no prior cytotoxic treatment, good performance status and high dosages of the

drug. Therefore we must conclude that mitoxantrone has no role to play in the treatment of advanced renal cell cancer. The search for other new and, hopefully, more active drugs will be continued.

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